HAMILTON
BROOK
SMITH &
REYNOLDS, P.C.

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TWO MILITIA DRIVE
LEXINGTON, MA
02421-4799
TEL (781) 861-6240
FAX (781) 861-9540
www.hbsr.com

September 3, 1999 Ext. of Time (4th)
Grn 09/10/99

Assistant Commissioner for Patents
Box AF
Washington, D.C. 20231

Re: Appellants: Marc Feldmann and Ravinder N. Maini
Application No.: 08/690,775
Filed: August 1, 1996
Title: Anti-TNF Antibodies and Methotrexate in the Treatment of Autoimmune Disease
Docket No.: KIR92-01A4

Sir:

Transmitted herewith are three (3) originally signed copies of a Brief on Appeal for filing in the subject application. The Brief on Appeal is filed pursuant to the Notice of Appeal received by the U.S. Patent and Trademark Office on March 3, 1999.

1. [X] Appellants hereby petition to extend the time for filing a Brief on Appeal for four months from May 3, 1999 to September 3, 1999.

2. [ ] A [ ] month extension of time to extend the time for filing a Brief on Appeal from [ ] to [ ] was filed on [ ] with payment of a $[ ] fee.

[ ] Appellant hereby petitions for an additional [ ] month extension of time for filing a Brief on Appeal from [ ] to [ ].

3. [ ] An Oral Hearing before the Board of Patent Appeals and Interferences is respectfully requested.

4. Fees are submitted for the following:

[X]	Extension of Time for four months		$ 1360
[ ]	Additional Extension of Time:		
	Fee for Extension ([ ] mo.)	$	
	Less fee paid ([ ] mo.)	- $	
	Balance of fee due		$ 0
[ ]	Oral Hearing		$
[X]	Brief on Appeal		$ 300
[ ]	Other _____		$
		TOTAL	$ 1660

5. The method of payment for the total fees is as follows:

[X] A check in the amount of $1,660.00 is enclosed.

[ ] Please charge Deposit Account No. 08-0380 in the amount of $[ ].

Please charge Deposit Account No. 08-0380 for any additional amounts that may be due in this matter. A copy of this letter is enclosed for accounting purposes.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Helen Lee

Helen Lee
Registration No. 39,270
Telephone: (781) 861-6240
Facsimile: (781) 861-9540

Dated: September 3, 1995

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PATENT APPLICATION
Docket No.: KIR92-01A4

#19

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellants: Marc Feldmann and Ravinder N. Maini

Application No.: 08/690,775 Group Art Unit: 1644

Filed: August 1, 1996 Examiner: P. Gambel

For: ANTI-TNF ANTIBODIES AND METHOTREXATE IN THE TREATMENT OF AUTOIMMUNE DISEASE

CERTIFICATE OF MAILING
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231
on 9-3-99 Sandra Vautour
Date Signature
Sandra Vautour
Typed or printed name of person signing certificate

BRIEF ON APPEAL

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Brief on Appeal is submitted pursuant to the Notice of Appeal mailed on March 1, 1999 and received in the U.S. Patent and Trademark Office on March 3, 1999, in the above-referenced patent application. The fee for filing this Brief on Appeal is enclosed. A four-month

extension of time for submission of this Brief is requested. A Petition for Extension of Time and the appropriate fee are being filed concurrently with this Brief.

This Brief is submitted in support of the appeal of the Examiner's final rejection of Claims 1, 5-10, 13-18 and 21-31 as set forth in the Office Action made final, which was mailed from the Patent Office on September 1, 1998.

Each of the requirements set forth in 37 C.F.R. § 1.192(c) follows under the separate headings.

I. REAL PARTY OF INTEREST

The real parties of interest are the Kennedy Institute of Rheumatology, One Aspenlea Road, Hammersmith, London W6 8LH, England, pursuant to assignments from each of the inventors of the subject application, and Centocor, Inc., 200 Great Valley Parkway, Malvern, Pennsylvania 19355, licensee of the subject matter described in the subject application.

II. RELATED APPEALS AND INTERFERENCES

Appellants, the undersigned Attorney, Assignee and Licensee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 1, 5-10, 13-18 and 21-31 are pending and subject to this appeal. Claims 2, 3, 11, 12, 19 and 20 were cancelled by Appellants in Amendment B, filed June 8, 1998. Claim 4 was cancelled by Appellants in Amendment A, filed September 3, 1997. The pending claims, as they stood upon final rejection, are presented in the Appendix to this Brief.

IV. STATUS OF AMENDMENTS

No Amendments have been filed subsequent to the mailing of the Office Action made final dated September 1, 1998 (Paper No. 15). All Amendments filed in this application have been entered.

V. SUMMARY OF INVENTION

The present invention relates to the discovery that a TNFα antagonist can be administered to patients suffering from a TNF-mediated disease (such as an autoimmune or inflammatory disease) as adjuvant or concomitant therapy to methotrexate therapy, with a rapid and sustained reduction in the clinical signs and symptoms of the disease. The present invention also relates to the unexpected discovery that a multiple dose regimen of a TNFα antagonist can be administered to patients suffering from a TNF-mediated disease as adjuvant or concomitant therapy to methotrexate therapy, with a highly beneficial or synergistic clinical response for a significantly longer duration compared to that obtained with a single or multiple dose regimen of the antagonist administered alone or that obtained with methotrexate administered alone.

Thus, the present invention relates to methods of treating an autoimmune or inflammatory disease in an individual in need thereof comprising co-administering therapeutically effective amounts of methotrexate and a TNF alpha antagonist (Claim 31), such as an anti-TNFα antibody or antigen-binding fragment thereof (Claims 1 and 5-9), to the individual.

The present invention also relates to methods of treating rheumatoid arthritis (Claims 10 and 13-17) or Crohn's disease (Claims 18 and 21-25) in an individual in need thereof comprising co-administering therapeutically effective amounts of methotrexate and an anti-TNFα antibody or antigen-binding fragment thereof to the individual.

The present invention further relates to compositions comprising methotrexate and an anti-TNFα antibody or antigen-binding fragment thereof (Claims 26-30).

The antibody can be administered in multiple doses (Claims 5-9, 13-17 and 21-25). The antibody can be a chimeric antibody (Claims 6-9, 14-17, 22-25 and 27-30). The antibody can bind to one or more epitopes included in amino acid residues of about 87-108 or about 59-80 of hTNFα (Claims 7, 15, 23 and 28) or competitively inhibit binding of TNFα to monoclonal antibody cA2 (Claims 8, 9, 16, 17, 24, 25, 29 and 30). In a particular embodiment, the antibody is cA2 (Claims 9, 16, 25 and 30).

VI. ISSUES

The following issues are on appeal:

(1) Whether the subject application is entitled to a priority date of October 8, 1992, the filing date of U.S. Application No. 07/958,248 (the '248 application).

(2) Whether Claims 1, 5-9 and 31 are properly rejected under 35 U.S.C. § 112, first paragraph, as non-enabling with respect to the breadth of autoimmune or inflammatory diseases treated with a combination of anti-TNFα antibody and methotrexate.

(3) Whether Claims 1, 5-10, 13-18 and 21-31 are properly rejected under 35 U.S.C. § 103 as obvious in view of Le *et al.* (U.S. Patent No. 5,656,272) and Aggarwal *et al.* (U.S. Patent No. 5,672,347) in view of Barrera *et al.* (*Cytokine, 3*(5):504, Abstract 330 (1991)), Kozarek *et al.* (*Ann. Int. Med., 110*:353-356 (1989)), Markowitz *et al.* (*J. Ped. Gastroent. Nutr., 12*:411-423 (1991)), Brahn *et al.* (*Arth. Rheum.*, 32(Suppl. 4):S133, Abstract D42 (1992)), Cohen *et al.* (*Rev. Esp. Rheumatol., 20*(Suppl. 1):148, Abstract 318 (1993)), and Pascalis *et al.* (*Rev. Esp. Rheumatol., 20*(Suppl. 1):148, Abstract 319 (1993)).

VII. GROUPING OF CLAIMS

With respect to the rejection designated as issue number (1), the claims stand or fall together. With respect to the rejection designated as issue number (2), the claims stand or fall together. With respect to the rejection designated as issue number (3), Claims 10, 14-17 do not stand or fall with the remaining claims. Also with respect to the rejection designated as issue number (3), Claims 26-30 do not stand or fall with the remaining claims.

VIII. APPELLANTS' ARGUMENT

Issue 1:

The Examiner has disputed whether the subject application is entitled to a priority date of October 8, 1992, the filing date of U.S. Application No. 07/958,248 (hereinafter "the '248 application"), stating that Appellants have "pointed out support for certain limitations of the instant claims to USSN 07/958,248", but have "not pointed out support for other limitations of the instant claims." Office Action dated September 1, 1998 (Paper No. 15), at page 2, paragraph 4.

It is Appellants' position that the pending claims are entitled to a priority date of October 8, 1992, the filing date of the '248 application. It is well settled that for sufficiency of support in a parent application, the subject matter of a claim need not be described literally (i.e., using the same terms or *in haec verba*).

The '248 application, at page 4, lines 27-32, describes the treatment of autoimmune disease and inflammatory disease (such as rheumatoid arthritis) with anti-CD4 antibodies and anti-TNF antibodies (see also, e.g., page 6, lines 5-8). At page 11, line 17 to page 12, line 4, the '248 application describes autoimmune and acute and chronic inflammatory diseases, specifically listing Crohn's disease and rheumatoid arthritis. At page 10, lines 6-9, the '248 application specifically recites the use of methotrexate in conjunction with an anti-TNF antibody. At page 6, lines 8 to page 7, line 26, the '248 application describes anti-TNF antibodies (see also page 8, lines 13-33).

The terms TNF and TNFα are used interchangeably in the art. See, e.g., Abbas *et al.*, *Cellular and Molecular Immunology*, 3rd edition, Philadelphia: W.B. Saunders Co., p. 258 (1997); attached hereto as the Exhibit 1. Thus, a person skilled in the art would, in the context of the subject application, interpret the term anti-TNF antibody to mean an anti-TNFα antibody. No evidence to the contrary has been presented. Indeed, the references incorporated by reference at page 8, lines 13-33 of the '248 application disclose anti-TNFα antibodies.

At page 8, line 16-17, the '248 application incorporates by reference U.S. Application No. 07/943,852, filed September 11, 1992, which application specifically discloses anti-TNF

antibodies that bind to one or more epitopes included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of hTNFα, anti-TNF antibodies that competitively inhibit binding of TNFα to monoclonal antibody cA2, and monoclonal antibody cA2. As such, the '248 application describes anti-TNF antibodies that bind to one or more epitopes included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of hTNFα, anti-TNF antibodies that competitively inhibit binding of TNFα to monoclonal antibody cA2, and monoclonal antibody cA2.

At page 11, lines 1-6, the '248 application describes the use of other agents which interfere with TNF, TNF receptor signalling or TNF synthesis (TNF antagonists).

At page 5, lines 4-6 and page 9, line 24-26, the '248 application provides that administration can be in the form of a single dose, or "a series of doses separated by intervals of days or weeks". One skilled in the art would reasonably interpret "a series of doses separated by intervals of days or weeks" to mean "multiple doses". No evidence to the contrary has been presented. At page 9, lines 1-23, the '248 specification provides guidelines for route of administration and dosages. Please note that, contrary to the Examiner's assertion, the pending claims do not recite the limitations "simultaneously" or "sequentially".

Thus, the '248 specification provides adequate support under 35 U.S.C. § 112 for the pending claims. Accordingly, the claims are entitled to a priority date of October 8, 1992, the filing date of the '248 application.

The Examiner has also disputed whether the claim limitations of "binds to one or more epitopes included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of hTNFα", "competitively inhibits binding of TNFα to monoclonal antibody cA2", "monoclonal antibody cA2", and "multiple doses" are supported by prior applications U.S. Application No. 08/403,785 (now U.S. Patent No. 5,741,488; hereinafter "the '488 patent") and International Application No. PCT/GB94/00462. Paper No. 15, at page 2.

It is Appellants' position that the recited claim limitations ("binds to one or more epitopes included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of hTNFα", "competitively inhibits binding of TNFα to monoclonal antibody cA2", "monoclonal

antibody cA2", and "multiple doses") are also supported by the '488 patent and by International Application No. PCT/GB94/00462.

The '488 patent and International Application No. PCT/GB94/00462 both incorporate by reference U.S. Application No. 07/943,852, which, as discussed above, specifically discloses anti-TNF antibodies that bind to one or more epitopes included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of hTNFα, anti-TNF antibodies that competitively inhibit binding of TNFα to monoclonal antibody cA2, and monoclonal antibody cA2. As such, the '488 patent and International Application No. PCT/GB94/00462 describe anti-TNF antibodies that bind to one or more epitopes included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of hTNFα, anti-TNF antibodies that competitively inhibit binding of TNFα to monoclonal antibody cA2, and monoclonal antibody cA2.

Both the '488 patent and International Application No. PCT/GB94/00462 also provide that administration can be in the form of a single dose, or a series of doses separated by intervals of days or weeks. One skilled in the art would reasonably interpret "a series of doses separated by intervals of days or weeks" to mean "multiple doses". No evidence to the contrary has been presented.

Accordingly, both the '488 patent and International Application No. PCT/GB94/00462 also provide adequate support under 35 U.S.C. § 112 for the pending claims.

Issue 2:

Claims 1, 5-9 and 31 have been rejected under 35 U.S.C. § 112, first paragraph, because the Examiner contends that the specification does not enable any person skilled in the art to use the combination of anti-TNFα antibody and methotrexate to treat any autoimmune or inflammatory disease. The Examiner's position appears to be that it would require undue experimentation to practice the claimed invention with a reasonable expectation of success because of (1) the lack of predictability of the art; (2) the lack of established clinical protocols for effective anti-inflammatory therapies with anti-cytokine therapy commensurate in scope with the claimed methods and compositions; (3) the absence of a specific and detailed description in the

specification of how to effectively practice the claimed invention; and (4) the absence of working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting autoimmune or inflammatory diseases. Office Action dated December 9, 1997 (Paper No. 10), at page 3, paragraph 3. Appellants respectfully disagree.

The standard for enablement under 35 U.S.C. § 112, first paragraph, is whether the claimed invention can be practiced without undue experimentation given the guidance presented in the specification and what was known to the skilled artisan at the time the subject application was filed. A specification which contains a teaching of how to make and use the full scope of the claimed invention must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation. In re Borkowski, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). See also M.P.E.P. § 2164.02.

The specification teaches that autoimmune and inflammatory diseases can be treated in an individual by co-administering methotrexate and a TNFα antagonist, such as an anti-TNFα antibody, to the individual in therapeutically effective amounts. Examples of autoimmune and inflammatory diseases that can be treated are disclosed in the specification, for example, at page 8, line 28 to page 9, line 3 (i.e., Item A); and page 9, lines 12-27 (i.e., Item C). Examples of TNFα antagonists that can be used in the claimed invention, including anti-TNFα antibodies, are provided in the specification, for example, at page 12, line 29 to page 35, line 11). Guidelines for route of administration and dosages are provided in the specification, for example, at page 35, line 28 to page 39, line 26.

Appellants have exemplified the claimed methods using monoclonal anti-TNFα antibody cA2 in patients with active rheumatoid arthritis (see specification, e.g., Examples 1-3).

One skilled in the art would reasonably expect that the claimed methods work in the same manner for other autoimmune and inflammatory diseases, known to be mediated by TNFα, given the results disclosed in the specification for arthritis. Clinical results with anti-TNFα antibodies

and other TNFα antagonists have been successful in treating multiple autoimmune and inflammatory diseases. For example, the use of anti-TNFα antibodies in treating autoimmune diseases such as rheumatoid arthritis (RA) and Crohn's disease has been further supported by clinical data, as established by the Le *et al.* patent cited in the section 103 rejection below (U.S. Patent No. 5,656,272). No evidence to support the conclusion that the results described in the subject application cannot be extrapolated to these related diseases has been provided. Thus, Appellants respectfully submit that the guidance provided in the specification is sufficient to teach the skilled artisan how to use the full scope of the claimed methods without undue experimentation.

The Examiner pointed to Natanson *et al. (Ann. Int. Med., 120*(9):771-783 (1994)) as providing evidence that the skilled artisan would not be able "to predict the efficacy of targeting any TNF-mediated disease or inflammatory disease with any TNF-specific antibody and methotrexate". Paper No. 15, at page 3, paragraph 2, lines 5-9. The Examiner also noted that "there are distinct differences in the cytokine requirements for particular types of inflammation and distinct differences in the cytokine requirements for particular types of inflammation and distinct differences in diseases which can be targeted by anti-TNFα antibody and methotrexate." Paper No. 15, at page 3, paragraph 2, lines 10-12. It is believed that the Natanson *et al.* reference was cited by the Examiner as providing evidence that the skilled artisan would not readily accept that the specification provides enabling support for the full scope of Claims 1, 5-9 and 31.

Claims 1, 5-9 and 31 are limited to the treatment of autoimmune diseases and inflammatory diseases. The Examiner, referring to page 3, maintains that "the instant specification discloses that the instant inflammatory diseases encompass autoimmune diseases, viral, bacterial, parasitic infections, malignancies and neurogenerative diseases." Paper No. 15, at page 3, paragraph 3, last sentence. Appellants respectfully submit that the Examiner has misinterpreted the sentence at page 3, lines 20-25, relied upon to support this assessment.

The sentence at page 3, lines 20-25 of the specification discloses five categories of diseases in which TNFα has been implicated. More specifically, the sentence discloses that TNFα has been implicated (1) in inflammatory diseases, (2) in autoimmune diseases, (3) in viral, bacterial and parasitic infections, (4) in malignancies, and (5) in neurogenerative diseases.

Inflammatory diseases are defined in the subject specification to be TNF-mediated diseases (see page 9, Item C). Specific examples of inflammatory diseases are provided in the specification at page 9, lines 12-27 (i.e., Item C) and do not include "autoimmune diseases", "viral, bacterial and parasitic infections", "malignancies", and "neurogenerative diseases". In fact, "autoimmune diseases", "viral, bacterial and parasitic infections", "malignancies", and "neurogenerative diseases", are each separately defined in the subject specification to be TNF-mediated diseases (see pages 8 to 10, Item A for autoimmune diseases, Item B for infections, Item D for neurodegenerative diseases, Item E for malignancies).

Thus, both autoimmune diseases and inflammatory diseases belong to an art-recognized class and are known in the art, or are otherwise accepted by those skilled in the art, to be mediated by TNFα. The methods comprise co-administering methotrexate and an anti-TNFα antibody or other TNFα antagonist to the individual. The fact that the cytokine requirements for particular types of inflammation may be different is irrelevant to the issue. The claims do not embrace the treatment of diseases where TNFα does not play an important role in the disease. One skilled in the art would reasonably expect that the results exemplified in the specification for patients with RA are representative of results for patients with other autoimmune or inflammatory diseases in which TNFα plays an important role. That is, one skilled in the art would reasonably find the results exemplified in the specification for RA patients to be reasonably predictive of results for patients with other autoimmune or inflammatory diseases in which TNFα plays an important role. Thus, one skilled in the art would accept the assertions in the specification as true and enabling. No evidence to the contrary has been presented.

The Natanson *et al.* reference is cited by the Examiner as teaching that "anti-TNF was not beneficial in sepsis and septic shock and that targeting TNF [in sepsis] could be harmful." Paper No. 15, at page 3, paragraph 2. Sepsis and septic shock are defined in the subject specification at page 9, lines 4-6 (i.e., Item B), to be examples of "infections". Neither sepsis nor septic shock is defined in the subject specification to be an autoimmune disease (see pages 8-9, Item A) or an inflammatory disease (see page 9, Item C). Accordingly, the Natanson *et al.* reference is not relevant to the enablement of Claims 1, 5-9 and 31. Natanson *et al.* do not provide a sufficient basis to question the enablement provided in the subject specification for the claimed methods.

The Examiner has also maintained that:

> [A]lthough in vitro experimental studies and animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In vitro assays are conducted under controlled conditions which do not necessarily reflect the complexity of in vivo conditions. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Often the antagonist and the stimulus/insult are given at the same time. Immunosuppression is much easier to achieve under such controlled conditions than experienced in the human immunoregulatory diseases such as the acute and chronic immune diseases, autoimmune diseases, inflammatory diseases and neurodegenerative diseases targeted by the claimed invention.

Paper No. 10, at page 2, last paragraph.

It is believed that the unsupported assertions presented in this argument are also being relied upon as providing evidence that one skilled in the art would not readily accept that the specification provides enabling support for the full scope of the claimed invention. However, there is no nexus between these general scenarios envisioned by the Examiner and the human clinical data described in the subject application. In this instance, the use of antibodies in treating autoimmune diseases, such as RA and Crohn's disease, has been further supported by human clinical data. The possible difficulties which may be encountered in therapy have been rebutted by clinical data in patients after onset of disease. The extrapolation of animal data to the human condition has been validated with anti-TNFα antibody, particularly when the antibody is used in the mouse after onset of disease as one does in human patients. One skilled in the art would reasonably expect that the claimed invention would work in the same manner for other autoimmune and inflammatory diseases known to be mediated by TNFα. The general scenarios envisioned by the Examiner do not provide a sufficient basis to question the enablement provided in the subject specification for the claimed methods.

The Examiner has also expressed concern that "In human diseases, patients are treated generally after the onset of disease and not prior to disease." Paper No. 10, at page 2, last sentence. There is no nexus between this concern envisioned by the Examiner and the claimed methods. None of the claims relate to methods of preventing an autoimmune or inflammatory

disease. Thus, the Examiner's reliance on this argument is improper. The invention must be viewed for what is being claimed.

There is nothing of record which might suggest that the guidance provided in the specification would be insufficient to enable the skilled artisan to practice these claims without undue experimentation and with a reasonable expectation of success. Accordingly, Appellants submit that the specification enables one skilled in the art to use the combination of anti-TNFα antibody and methotrexate to treat autoimmune or inflammatory diseases without undue experimentation.

Issue 3:

Claims 1, 5-10, 13-18 and 21-31 have been rejected under 35 U.S.C. § 103 as unpatentable over Le *et al.* (U.S. Patent No. 5,656,272) and Aggarwal *et al.* (U.S. Patent No. 5,672,347) in view of Barrera *et al.* (*Cytokine, 3*(5):504 (1991), Abstract 330), Kozarek *et al.* (*Ann. Int. Med., 110*:353-356 (1989)), Markowitz *et al.* (*J. Ped. Gastroent. Nutr., 12*:411-423 (1991)), Brahn *et al.* (*Arth. Rheum.*, 32(Suppl. 4):S133 (1992), Abstract D42), Cohen *et al.* (*Rev. Esp. Rheumatol., 20*(Suppl. 1):148 (1993), Abstract 318), and Pascalis *et al.* (*Rev. Esp. Rheumatol., 20*(Suppl. 1):148 (1993), Abstract 319). For purposes of this rejection, Claims 10, 14-17 do not stand or fall with the remaining claims. Claims 26-30 also do not stand or fall with the remaining claims. Claims 1, 5-9 and 31 relate to methods of treating any autoimmune or inflammatory disease. Claims 10 and 13-17 relate to methods of treating rheumatoid arthritis. Claims 18 and 21-25 relate to methods of treating Crohn's disease. Claims 26-30 relate to compositions comprising methotrexate and an anti-TNFα antibody or antigen-binding fragment thereof.

The Primary References

Le *et al.*

Le *et al.* disclose the use of TNF antagonists in the treatment of TNF-related pathologies, including rheumatoid arthritis, Crohn's pathology and ulcerative colitis. Le *et al.* further disclose

that the TNF antagonists can be administered either as individual therapeutic agents or in combination with other therapeutic agents (Le *et al.*, col. 35, l. 25-28).

Several clinical studies are described in the cited patent in which patients with rheumatoid arthritis (RA), Crohn's disease or ulcerative colitis were treated with an anti-TNFα antibody (see Le *et al.*, col. 58 to col. 79 (Examples XX to XXIII)). The patients employed in the trials described in Examples XX and XXII are said to have had a history of *failed* therapy with standard disease-modifying anti-rheumatic drugs (DMARDS), including methotrexate (Le *et al.*, col. 59, l. 4-6; col. 68, l. 35-36). Moreover, all DMARDS, including methotrexate, are said to have been discontinued at least one month prior to treatment with anti-TNFα antibody (see Le *et al.*, e.g., col. 71, l. 43-44; see also Tables 5, 6 and 12). Thus, Le *et al.* do not, and cannot, teach or suggest the therapeutic co-administration of a TNFα antagonist and methotrexate to an individual. In fact, the teachings of Le *et al.* would not have led one skilled in the art to reasonably conclude that it would be therapeutically beneficial to administer an ineffective drug with an effective drug. Le *et al.* also do not, and cannot, teach or suggest compositions comprising methotrexate and an anti-TNFα antibody or antigen-binding fragment thereof.

Aggarwal *et al.*

Aggarwal *et al.* disclose the administration of specific TNF antagonists in therapeutically effective amounts in the treatment of inflammatory or immune-potentiated inflammatory events (e.g., graft versus host reaction, arthritis, Crohn's disease) (Aggarwal *et al.*, col. 1, l. 18-24). Aggarwal *et al.* suggest that these TNF antagonists can be used in conjunction with other anti-inflammatory agents in the treatment of inflammatory or immune-potentiated inflammatory events (e.g., graft versus host reaction, arthritis, Crohn's disease) (Aggarwal *et al.*, col. 7, l. 60-63) and that "when employed together with TNF antagonists these agents may be employed in lesser dosages than when used alone" (Aggarwal *et al.*, col. 7, l. 65-67). Gold colloids, cyclosporin antibiotics, salicylate and corticosteroids (such as methylprednisolone) are listed in the cited patent as examples of "other anti-inflammatory agents" (Aggarwal *et al.*, col. 7, l. 63-64). Methotrexate is not set forth in the Aggarwal *et al.* patent as a therapeutic agent to co-administer with the TNF antagonists. As such, Aggarwal *et al.* do not teach or suggest the

therapeutic administration of a TNF antagonist in combination with methotrexate. Aggarwal *et al.* also do not teach or suggest compositions comprising methotrexate and an anti-TNFα antibody.

The Secondary References

Barrera *et al.*

Barrera *et al.* disclose in their abstract the use of low-dose methotrexate for treating patients with rheumatoid arthritis. They report that "three patients with highest values of stimulated IL-1β and TNF showed a decrease of more than 50% after MTX" (Barrera *et al.*, second sentence from end). Barrera *et al.* conclude that low-dose methotrexate treatment "*seems* to induce changes in IL-1β and TNF production in some RA patients" (Barrera *et al.*, last sentence, emphasis added).

Kozarek *et al.*

Kozarek *et al.* report the results of an open-label study of methotrexate treatment in patients with refractory inflammatory bowel disease, including Crohn's disease. They found that methotrexate induced clinical and histologic remission in some patients.

Markowitz *et al.*

The Markowitz *et al.* reference is cited by the Examiner as teaching "targeting TNF (page 413) and the use of methotrexate (page 421) in the treatment of inflammatory bowel diseases".

At page 413, Markowitz *et al.* state that "TNF appears to be a proximal mediator of inflammation and shock." This, however, does not teach, with an expectation of success, "targeting TNF" in the treatment of inflammatory bowel diseases. In addition, although Markowitz *et al.* disclose the use of methotrexate in the treatment of inflammatory bowel disease, they do not teach or suggest co-administering a TNF antagonist and methotrexate to treat the disease. Thus, Markowitz *et al.* do not teach or suggest, with an expectation of success,

treating inflammatory bowel disease (or other autoimmune or inflammatory disease, including rheumatoid arthritis) in an individual by co-administering methotrexate and a TNFα antagonist to the individual.

Brahn *et al.*

Brahn *et al.* disclose in their abstract the results from a study on the effects of TNFα, methotrexate, or combination cyclosporin and methotrexate therapy on collagen arthritis. They report that (1) TNFα therapy is "not therapeutically beneficial and may actually exacerbate collagen arthritis"; (2) methotrexate therapy is ineffectual at treating collagen arthritis; and (3) combination cyclosporin and methotrexate therapy attenuates the disease. Thus, Brahn *et al.* clearly teach away from the claimed invention.

Cohen *et al.*

Cohen *et al.* disclose the use of cyclosporine A or methotrexate in the treatment of patients with refractory rheumatoid arthritis (i.e., patients who had failed at least one DMARD).

Pascalis *et al.*

Pascalis *et al.* disclose the use of combined cyclosporine A, fluocortolone and methotrexate in the treatment of patients with rheumatoid arthritis resistant to conventional therapy.

The Combination of References

A *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable expectation of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in Appellants' disclosure. Id.

None of the cited references, alone or in combination, would have suggested the claimed methods to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. More specifically, none of the cited references, alone or in combination, would have suggested the therapeutic administration of an anti-TNFα antibody (or other TNFα antagonist) in combination with methotrexate to one of ordinary skill in the art at the time the invention was made with a reasonable expectation of success. As discussed above, Le *et al.* teach the use of TNF antagonists in the treatment of TNF-related pathologies, including rheumatoid arthritis, Crohn's pathology and ulcerative colitis and disclose that the TNF antagonists can be administered either as individual therapeutic agents or in combination with other therapeutic agents (Le *et al.*, col. 35, l. 25-28). Aggarwal *et al.* teach the administration of specific TNF antagonists in therapeutically effective amounts in the treatment of inflammatory or immune-potentiated inflammatory events (e.g., graft versus host reaction, arthritis, Crohn's disease) (Aggarwal *et al.*, col. 1, l. 18-24) and suggest that these TNF antagonists can be used in conjunction with other anti-inflammatory agents (e.g., gold colloids, cyclosporin antibiotics, salicylate and corticosteroids, such as methylprednisolone) (Aggarwal *et al.*, col. 7, l. 60-63). Neither the Le *et al.* patent nor the Aggarwal *et al.* patent suggests methotrexate as a therapeutic agent to co-administer with TNF antagonists.

Several of the secondary references (Barrera *et al.*, Kozarek *et al.*, Markowitz *et al.*, Brahn *et al.* and Cohen *et al.*) report the use of methotrexate alone in the treatment of autoimmune diseases, including rheumatoid arthritis and inflammatory bowel disease. Of these references, successful treatment with methotrexate is reported in the Barrera *et al.*, Kozarek *et al.*, Markowitz *et al.* and Cohen *et al.* references. In contrast, Brahn *et al.* report methotrexate therapy to be ineffective in treating arthritis. Thus, four of the secondary references cited by the Examiner report that therapy with methotrexate alone is effective in the treatment of autoimmune diseases; one of the secondary references cited by the Examiner reports that therapy with methotrexate alone is ineffective in treating arthritis.

Brahn *et al.* also report that the use of a *combination* of methotrexate and cyclosporin attenuates arthritis. In contrast, Pascalis *et al.* report efficacy in the use of a *combination* of methotrexate, fluocortolone and cyclosporin in treating rheumatoid arthritis. Thus, the Examiner

has cited one reference reporting the ineffectiveness of treating arthritis with methotrexate in a particular combination (i.e., methotrexate in combination with cyclosporin) and one reference reporting the efficacy of treating arthritis with methotrexate in another different combination (i.e., methotrexate in combination with cyclosporin and fluocortolone).

None of the secondary references (Barrera *et al.*, Kozarek *et al.*, Markowitz *et al.*, Brahn *et al.*, Cohen *et al.* and Pascalis *et al.*), alone or in combination, teach or suggest the therapeutic administration of a TNF antagonist in combination with methotrexate. As such, the secondary references do not cure the deficiencies of the Le *et al.* patent and the Aggarwal *et al.* patent. teach or suggest treating rheumatoid arthritis, Crohn's disease or other autoimmune or inflammatory disease in an individual by co-administering methotrexate and a TNFα antagonist to the individual.

Accordingly, the cited references, either alone or in combination, would not have suggested the claimed methods to one of ordinary skill in the art, at the time the invention was made, with a reasonable expectation of success.

The Examiner stated in Paper No. 10 that:

> The combination of references provide an expectation of success in combining various compositions to form a third composition to most effectively induce the appropriate immunosuppression for a targeted condition.

Paper No. 10, at page 6, paragraph 6, lines 5-7. Appellants respectfully disagree with this assessment. The Examiner has identified no suggestion in the prior art of the desirability of the proposed combination. The Examiner has identified no suggestion in the prior art that supports a reasonable expectation of success of producing the claimed invention. The cited references merely indicate that isolated elements and/or features recited in the claims are known. In fact, Brahn *et al.* clearly teach away from the proposed combination.

The Examiner also stated in Paper No 10 that:

> One of ordinary skill in the art at the time the invention was made would have been motivated to combine targeting the different elements contributing to inflammatory responses including those associated with arthritis and Crohn's disease. The art teaches that targeting TNF can all diminish the activity of

> inflammatory responses, including the use of either TNF-specific agents such as TNF-specific chimeric antibodies or an anti-inflammatory agent such as methotrexate. Combination therapies were well known in the art and both methotrexate and anti-TNF antibodies were shown to be effective in vivo. It was prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980.

Paper No. 10, at page 6, paragraph 7.

The Examiner appears to suggest that once two drugs are shown to be effective in treating a particular disease, their combination must necessarily be effective in treating the same disease. However, the Brahn *et al.* and Pascalis *et al.* references, which are discussed above, provide evidence that this is not the case. More specifically, Brahn *et al.* report the *ineffectiveness* of treating arthritis with methotrexate in combination with cyclosporin. In contrast, Pascalis *et al.* report the efficacy of treating arthritis with methotrexate in combination with cyclosporin and fluocortolone.

In Paper No. 15, the Examiner pointed to Borigini *et al.* (*Bailliere's Clinical Rheumatology, 9*(4):689-710 (1995)) as providing evidence that "the ordinary artisan was motivated with an expectation of success in combining conventional therapies with agents that inhibit specific events in inflammation." Paper No. 15, at page 4, paragraph 3. However, the totality of the plain language of the cited reference supports a contrary conclusion.

For example, although Borigini *et al.* disclose that "combination DMARD therapy is a useful tool in current rheumatological practice", they state that "well-designed, large, long-term, controlled clinical trials are needed to determine which combinations, dosage schedules, and sequences of administration are the most beneficial and least toxic" (Borigini *et al.*, sentence bridging pages 706 and 707). On page 707, Borigini *et al.* report that combinations which include anti-TNFα agents "have not yet been evaluated, although it seems logical considering that these agents offer the *possibility* of precise intervention directed at specific steps of the immuno-inflammatory process" and speculate that "their combination *may* thus be more effective than the use of single agents alone" (Borigini *et al.*, page 707, lines 40-45; emphasis added).

In Table 1, Borigini *et al.* report results of combination therapy in rheumatoid arthritis. Some drug combinations are said to be of no advantage, other combinations are said to be more effective than one or more individual drugs in the combination (Borigini *et al.*, page 694, Table 1). Thus, Borigini *et al.* provide additional evidence that the combination of two drugs shown to be effective individually in treating a particular disease may not necessarily be effective in treating the same disease.

Williams *et al.* (*Arthritis Rheum.*, 35(3):259-269 (1992) (attached as Exhibit 2)) report that combination therapy with methotrexate and auranofin, shown to be effective individually in the treatment of RA, did not demonstrate any advantage in efficacy over either drug given singly. Thus, Williams *et al.* provide further evidence that the combination of two drugs shown to be effective individually in treating a particular disease may not necessarily be effective in treating the same disease.

Accordingly, one of ordinary skill in the art would not have been able to predict, given the primary and secondary references cited in the rejection, whether co-administration of methotrexate and an anti-TNFα antibody or other TNFα antagonist to an individual would be effective in methods for treating rheumatoid arthritis, Crohn's disease or other autoimmune or inflammatory diseases.

The only document of record in this prosecution which suggests the desirability of the combination proposed by the Examiner is Appellants' specification. However, the use of the claimed invention as an instruction manual or template to piece together the teachings of the prior art is impermissible hindsight.

Thus, Claims 1, 5-10, 13-18, 21-25 and 31 are nonobvious over the cited references and their combination(s).

Notwithstanding the above, it is by now well settled that significant improvements in combination therapies can rebut a *prima facie* case of obviousness. See In re Kollman, 201 U.S.P.Q. 193 (C.C.P.A. 1979). See also M.P.E.P. § 716.02(a). Greater than expected results is evidence of nonobviousness. See, e.g., M.P.E.P. § 716.02(a). Evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating synergism). Merck & Co. Inc. v. Biocraft

Laboratories Inc., 10 U.S.P.Q.2d 1843 (Fed. Cir. 1989), *cert. denied*, 493 U.S. 975 (1989); In re Luvisi and Nohejl, 144 U.S.P.Q. 646 (C.C.P.A. 1965).

Appellants demonstrated the unexpected result that combination therapy with methotrexate and a TNFα antagonist produced unexpected synergistic effects between methotrexate and the TNFα antagonist (see, e.g., Figures 1A, 2A, 3A, 4A, 5A and Table 4 of the specification). Appellants also demonstrated the unexpected result that significantly reduced immunogenicity of anti-TNFα antibodies was obtained with combination therapy with methotrexate (see, e.g., page 57, line 30 to page 60, line 4, including Table 6, of the specification). Appellants further demonstrated the unexpected result that combination therapy with methotrexate and a TNFα antagonist produced high clinical response rates for significantly longer durations in comparison with that obtained with treatment with each therapeutic modality separately (see specification, e.g., page 4, lines 8-18; Examples 1-3, particularly, page 48, lines 6-11, page 51, lines 1-4, pages 49-50 (Table 3), pages 52-53 (Table 4), page 62, line 17 to page 63, line 10 of Example 1; page 65, line 6 to page 66, line 32 of Example 2; and page 68, line 12 to page 69, line 14 of Example 1). The magnitude of these results, particularly in the treatment of RA, could not have been predicted from the cited references.

For example, although Le *et al.* state that TNF antagonists can be administered either as individual therapeutic agents or in combination with other therapeutic agents (Le *et al.*, col. 35, l. 25-28), this would not have led one of ordinary skill in the art to expect that such administration would produce the results described in the subject application, particularly synergistic effects. Similarly, although the Aggarwal *et al.* patent indicates that when employed together, TNF antagonists and other anti-inflammatory agents (e.g., cyclosporin) can be administered in lesser dosages than when used alone (Aggarwal *et al.*, col. 7, l. 65-67), this would not have led one of ordinary skill in the art to expect that such administration would produce synergistic effects.

None of the secondary references cited by the Examiner (Barrera *et al.*, Kozarek *et al.*, Markowitz *et al.*, Brahn *et al.*, Cohen *et al.*, and Pascalis *et al.*) would have led one of ordinary skill in the art to expect that the results described in the subject application, particularly synergistic effects, would be obtained by combination therapy with methotrexate and a TNFα

antagonist. In fact, Brahn *et al.*, who disclose that combination cyclosporin and methotrexate therapy attenuates arthritis, clearly teach away from the claimed invention.

Thus, the cited references in combination also would not have led one of ordinary skill in the art to expect that synergistic effects would be obtained by combination therapy with methotrexate and a TNFα antagonist, particularly in the treatment of RA.

With regard to Claims 26-30, none of the cited references teach or suggest a composition comprising methotrexate and an anti-TNFα antibody. The Examiner has identified no suggestion in the prior art of the desirability of the proposed combination of references to produce the claimed compositions. The only document of record which suggests the desirability of the combination proposed by the Examiner is Appellants' specification. However, the use of the claimed invention as an instruction manual or template to piece together the teachings of the prior art is impermissible hindsight. Accordingly, Claims 26-30 are nonobvious over the cited references and their combination(s).

CONCLUSION

It is respectfully requested that the rejections be reversed and that the claims be allowed. This Brief is being filed in triplicate.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Helen Lee

Helen Lee
Registration No. 39,270
Telephone: (781) 861-6240
Facsimile: (781) 861-9540

Lexington, MA 02421-4799

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APPENDIX

REJECTED CLAIMS OF 08/690,775

1. A method of treating an autoimmune or inflammatory disease in an individual in need thereof comprising co-administering methotrexate and an anti-tumor necrosis factor alpha antibody or antigen-binding fragment thereof to the individual, in therapeutically effective amounts.

5. A method of Claim 1 wherein the anti-tumor necrosis factor alpha antibody is administered in multiple doses.

6. A method of Claim 5 wherein the anti-tumor necrosis factor alpha antibody is a chimeric antibody.

7. A method of Claim 6 wherein the chimeric antibody binds to one or more epitopes included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of hTNFα.

8. A method of Claim 6 wherein the chimeric antibody competitively inhibits binding of TNFα to monoclonal antibody cA2.

9. A method of Claim 8 wherein the chimeric antibody is monoclonal antibody cA2.

10. A method of treating rheumatoid arthritis in an individual in need thereof comprising co-administering methotrexate and an anti-tumor necrosis factor alpha antibody to the individual, in therapeutically effective amounts.

13. A method of Claim 10 wherein the anti-tumor necrosis factor alpha antibody is administered in multiple doses.

14. A method of Claim 13 wherein the anti-tumor necrosis factor alpha antibody is a chimeric antibody.

15. A method of Claim 14 wherein the chimeric antibody binds to one or more epitopes included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO:2) of hTNFα.

16. A method of Claim 14 wherein the chimeric antibody competitively inhibits binding of TNFα to monoclonal antibody cA2.

17. A method of Claim 16 wherein the chimeric antibody is monoclonal antibody cA2.

18. A method of treating Crohn's disease in an individual in need thereof comprising co-administering methotrexate and an anti-tumor necrosis factor alpha antibody to the individual, in therapeutically effective amounts.

21. A method of Claim 18 wherein the anti-tumor necrosis factor alpha antibody is administered in multiple doses.

22. A method of Claim 21 wherein the anti-tumor necrosis factor alpha antibody is a chimeric antibody.

23. A method of Claim 22 wherein the chimeric antibody binds to one or more epitopes included in amino acid residues of about 87-108 (SEQ ID N:1) or about 59-80 (SEQ ID NO:2) of hTNFα.

24. A method of Claim 22 wherein the chimeric antibody competitively inhibits binding of TNFα to monoclonal antibody cA2.

25. A method of Claim 22 wherein the chimeric antibody is monoclonal antibody cA2.

26. A composition comprising methotrexate and an anti-tumor necrosis factor alpha antibody or antigen-binding fragment thereof.

27. A composition of Claim 26 wherein the anti-tumor necrosis factor alpha antibody is a chimeric antibody.

28. A composition of Claim 27 wherein the chimeric antibody binds to one or more epitopes included in amino acids of about 87-108 and about 59-80 of hTNFα.

29. A composition of Claim 27 wherein the chimeric antibody competitively inhibits binding of TNFα to monoclonal antibody cA2.

30. A composition of Claim 29 wherein the chimeric antibody is monoclonal antibody cA2.

31. A method of treating an autoimmune or inflammatory disease in an individual in need thereof comprising co-administering methotrexate and a tumor necrosis factor alpha antagonist to the individual, in therapeutically effective amounts.